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Strength Training to Enhance Early Recovery after Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Intensive cancer treatment followed by hematopoietic stem cell transplantation (HCT) results in moderate to severe fatigue and physical inactivity, leading to diminished functional ability. The purpose of this study was to determine the efficacy of an exercise intervention, strength training to enhance early recovery (STEER), on physical activity, fatigue, muscle strength, functional ability, and quality of life after HCT. This single-blind, randomized clinical trial compared strength training (n = 33) to usual care plus attention control with health education (UC + AC with HE) (n = 34). Subjects were stratified by type of transplantation and age. STEER consisted of a comprehensive program of progressive resistance introduced during hospitalization and continued for 6 weeks after hospital discharge. Fatigue, physical activity, muscle strength, functional ability, and quality of life were assessed before HCT hospital admission and after intervention completion. Data were analyzed using split-plot analysis of variance. Significant time × group interactions effects were noted for fatigue ($P = .04$). The STEER group reported improvement in fatigue from baseline to after intervention whereas the UC + AC with HE group reported worsened fatigue from baseline to after intervention. Time ($P < .001$) and group effects ($P = .05$) were observed for physical activity. Physical activity declined from baseline to 6 weeks after hospitalization. The STEER group was more physically active. Functional ability tests (timed stair climb and timed up and go) resulted in a significant interaction effect ($P = .03$ and $P = .05$, respectively). Subjects in the UC + AC with HE group were significantly slower on both tests baseline to after intervention, whereas the STEER group's time remained stable. The STEER group completed both tests faster than the UC + AC with HE group after intervention. Study findings support the use of STEER after intensive cancer treatment and HCT. Strength training demonstrated positive effects on fatigue, physical activity, muscle strength, and functional ability. The exact recovery patterns between groups and over time varied; the STEER group either improved or maintained their status from baseline to after intervention (6 weeks after hospital discharge) whereas the health education group generally declined over time or did not change.

INTRODUCTION

Intensive cancer treatment followed by hematopoietic stem cell transplantation (HCT) is considered curative for a number of hematological malignancies [1] but it is associated with high 100-day treatment-related mortality [1] and devastating complications [2,3]. These complications result in highly distressing symptoms, significantly impaired functional status, and diminished quality of life (QOL) that can last for years after treatment [4-7]. A marked reduction in physical activity after intensive cancer treatment and HCT has been documented [8]. Up to 90% of HCT recipients report severe persistent fatigue [9-12]. Although the relationship between physical activity and fatigue is not completely understood, sustained physical inactivity after HCT is sufficient to cause loss of muscle mass with resulting decreases in strength. Muscle mass losses during the first 6 months after HCT are frequently not regained even 5 years after transplantation [13-15].

This clinical picture of impaired recovery after intensive cancer treatment and HCT closely resembles the clinical syndrome of frailty in older adults. Using Fried's Clinical Phenotype of Frailty in Older Adults [16] as a guide and adapted for HCT, we hypothesized that muscle strength plays a crucial role in preventing the development of physical deconditioning/frailty and eventual progression to disability in HCT recipients (Figure 1). The working hypothesis is that

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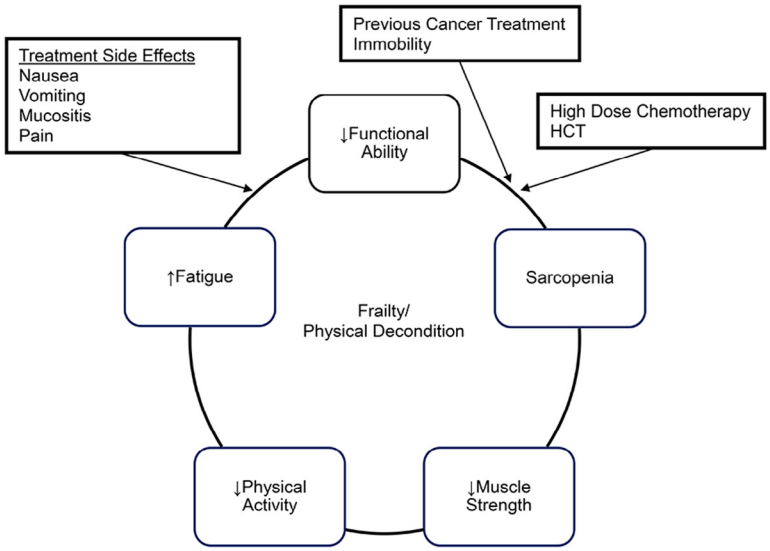

Figure 1. Model of frailty/physical decondition (adapted from Fried's Clinical Phenotype of Frailty in Older Adults, 2001).

muscle strength is needed to break the negative cycle of physical deconditioning/frailty that begins with loss of muscle mass leading to decreased strength→ reduced physical activity→ fatigue→ decreased functional ability→ even further loss of muscle mass. Without intervention, frailty and long-term disability ensue even though the HCT survivors are free of cancer [17]. Thus, there is a tremendous need to break this negative cycle and develop effective interventions to reduce loss of muscle mass and enhance early recovery.

This study focuses on strength training to enhance early recovery (STEER) after intensive cancer treatment and HCT. Exercise is widely promoted as a means for improving physical functioning in people with cancer [18,19]. Strength training, in comparison to all other exercise modalities, most effectively builds muscle mass [20]; however, few studies have evaluated strength training in the HCT population. Most HCT studies combined strength training with aerobic exercises [21-27], making it difficult to disentangle the individual effects of strength training. Only 1 small HCT study, besides our pilot work, employed single-modality strength training [28]. Although beneficial effects were demonstrated, fatigue, physical activity, and functional ability were not assessed. Our pilot studies demonstrated that (1) strength training using elastic resistance bands has potential positive effects on physical activity, fatigue, and QOL; and, (2) strength training is feasible during the early recovery period if the intervention is tailored to the individual's capabilities, making subject burden reasonable [29,30].

A strength training intervention to block or reverse physical deconditioning after HCT is vitally important for maintaining physical independence, as demonstrated by the ability to perform everyday activities. From a cost and subject burden perspective, it is imperative that the independent effects of strength training be established in this challenging population. Furthermore, strength training after HCT may be more important than aerobic exercise, according to the American College of Sports Medicine [31]. Given the importance of maintaining muscle mass and reducing the debilitating effects of intensive cancer treatment and HCT, there is a clear need for a randomized clinical trial (RCT) to evaluate a strength training intervention in the early recovery period after HCT. The purpose of this single-blind RCT was to compare STEER to usual care plus attention control with health education (UC + AC with HE) after intensive cancer treatment and HCT on physical activity, fatigue, muscle strength, functional ability, and QOL. This study addresses the following question, "Does strength training enhance recovery from baseline to 6 weeks after hospital discharge after HCT?"

METHODS

Design

This study employed a single-blind RCT to test the efficacy of the STEER invention compared with UC + AC with HE after HCT. Subjects were stratified by type of transplantation (allogeneic or autologous) and by age (≤60 years of age or > 60 years of age). Random allocation to treatment and allocation concealment were achieved using sequentially numbered, opaque, sealed envelopes [32].

STEER consisted of a comprehensive program of progressive resistance using elastic resistance bands to strengthen the upper body, lower body, and abdominal muscles. UC + AC with HE consisted of a standardized health education program. Both study arms contained an in-hospital component followed by a 6-week post–hospital discharge phase (described in detail below). Dependent variables included physical activity, fatigue, muscle strength, functional ability, and QOL. Variables were measured before admission to the hospital for the HCT to provide baseline information and during the seventh week after hospital discharge to provide information regarding the efficacy of the intervention and recovery after HCT. The study was approved by the institutional review board.

Sample and Setting

Consecutively eligible patients 18 years of age or older scheduled to undergo HCT at a Midwestern academic medical center were invited to participate. Patients who were initially eligible for inclusion were scheduled to undergo HCT for an underlying malignancy and cognitively able to understand the purpose of the research. Patients contemplating HCT undergo an extensive medical work-up before transplantation. All of the pretesting procedures are standard of care and were not considered part of the research. The medical work-up generally includes a history and physical; multigated acquisition scans to assess heart function; spirometry to assess pulmonary function; various blood tests to assess kidney, liver, and blood cell function and exposure to viruses; chest x-rays; urinalysis; and a dental exam. The treating physicians reviewed all the pretests and provided approval for subjects to participate in this study. Subjects were excluded if they presented with a significant comorbidity, such as impending pathological fracture, that would be make it potentially unsafe to exercise if randomized to STEER. To continue to participate in the study after hospital discharge, subjects were required to be ambulatory.

Enrollment was open from May 2013 through August 2015. One hundred eighteen people scheduled for HCT were eligible to participate. Eighty-four (71%) agreed to participate. Multiple reasons for declining to participate

were provided, including too much on their plate and not interested in participating in the study. Five of the 84 subjects who agreed to participate were withdrawn from the study before completion of any research activities. An additional 4 subjects were withdrawn from the study after completing baseline testing. These 9 subjects did not proceed to HCT. Seventy-five subjects were randomized (STEER group, n = 37; UC + AC with HE group, n = 38). Seven subjects expired before the end of the study and 1 was lost to follow-up (STEER group, n = 4; and UC + AC with HE group, n = 4). Sixty-seven subjects completed the study; thus, the study retained 89% of the subjects who initially enrolled and received a transplant. The primary reason for subject attrition was death and the death was attributable to the underlying medical condition.

Strength Training Intervention

The strength training intervention, STEER, consisted of a comprehensive program of progressive resistance to strengthen the upper body, lower body, and abdominal muscles using elastic resistance bands (Therabands, Hygenic Corp., Akron, OH) and body weight for resistance. Subjects received instruction and began active range of motion 2 times per week while hospitalized for HCT. Moderate-intensity strength training began immediately after discharge from the hospital. Hospital discharge was chosen as the time to initiate the moderate intensity training as HCT patients are generally considered medically stable; thus, it is a common safe point to initiate the intervention. Training continued 3 times per week for 6 weeks after hospital discharge. The Borg rating of perceived exertion scale, a 20-point scale, was used to estimate the intensity of the resistance [33]. The moderate-intensity strength training prescription was based on a rating of somewhat hard (Borg scale, 13). Instruction and training were conducted by the principal investigator or a trained member of the research team.

STEER consisted of 11 preselected exercises with concentric and eccentric muscle contractions as follows: (1) 8 exercises using elastic resistance bands (chest fly, biceps curl, triceps extension, shoulder shrug, shoulder upright row, shoulder lateral raise, knee flexion, and knee extension) and (2) 3 exercises that used body weight as resistance (wall push-ups, squats, and bed sit-ups). Some subjects were not able to perform all 11 exercises when the moderate-intensity strength training intervention was initiated after hospital discharge. As a result, the initial moderate-intensity exercise prescription required tailoring to the individual's capabilities. Subjects were prescribed as many exercises as they could perform, starting with the easiest exercises and advancing to the most difficult. Subjects provided return demonstrations of the exercises to ensure proper form and reduce the chance of injury. All subjects rated their strength training program as moderately hard, regardless of the number of exercises performed, resistance band used, and/or number of repetitions/sets performed.

The STEER intervention employed a supervised/unsupervised approach. Subjects were seen once or twice each week during their regularly scheduled clinic visit to exercise under the supervision of a member of the research team. These 1-on-1 sessions were conducted in clinic exam rooms. Changes to the exercise prescription, mostly advancements, were made at that time, facilitating progression with the exercise prescription. Progression of the exercise prescription was structured to first increase the number of repetitions, followed by increasing the number of sets from 1 to 2 sets, and finally increasing the resistance level of elastic bands. Subjects were encouraged to exercise on their own 2 more times during the week for a total of 3 times per week. Subjects documented completion of each individual exercise, including information about the number of repetitions and sets, on preprinted exercise logs. Subjects were queried regarding exercise adherence and tolerance to the exercise prescription during weekly clinic visits.

This clinic/home-based strength training program was chosen for multiple reasons: (1) reduces the risk of exposure to pathogens that may be acquired in other public places such as gyms; (2) reduces the burden of traveling to and from a gym or laboratory in patients who may be experiencing significant fatigue; (3) elastic resistance bands are portable and can be easily used in a clinic or home setting; (4) makes effective use of the time patients spend waiting in clinic to exercise under supervision; and (5) the equipment is affordable so the training program can easily be implemented on a larger scale if successful. Studies involving elastic resistance exercises demonstrate increased strength [34-37], improved function and decreased disability [38,39], and improved range of motion and flexibility [40]. Elastic resistance exercises have been used in a variety of populations, including multiple myeloma patients [22], the elderly [34,35], cardiac patients [41], and in our own pilot studies with HCT patients [29,30].

UC + AC with HE

The UC + AC with HE intervention was implemented in 2 phases, similar to the STEER intervention. During hospitalization for HCT, subjects in the UC + AC with HE group received 2 visits per week, during which they were given the opportunity to discuss the hospital experience. After hospital discharge, the 6-week health education program was implemented. The UC + AC with HE subjects were seen once each week in clinic during scheduled clinic appointments to deliver the standardized 1-on-1 education intervention. The intervention was delivered in the clinic exam rooms. Topics included protecting your health, working with your doctors, dealing with finances, and guides for recommended tests and procedures after HCT. Publicly available patient education materials from the Center for International Blood and Marrow Transplant Research and National Marrow Donor Program were used. Subjects received usual care recommendations regarding rest, physical activity, and exercise from their attending HCT physician. Subjects were not told that they could not exercise.

Instrumentation

Physical activity

Physical activity was objectively measured during waking hours using a wrist-worn accelerometer (primary aim), the Actical (Philips Respironics, Bend, OR) and through self-report (Godin leisure-time exercise questionnaire) [42]. The objectively measured physical activity data were analyzed using the Actical software (Version 3.0). The following criteria were met for inclusion in the data analysis: (1) at least 10 hours per day of physical activity data was provided during waking hours; and, (2) a minimum of 3 days of data were provided for both data collection periods (baseline and after intervention). The average physical count per minute is reported.

Accelerometry is a well-established method to assess physical activity. Intra- and interinstrument reliability were established using a shaker table under 6 different conditions of various intensity to produce a range of accelerometry counts [43]. Correlations with the maximal 6-minute walk ($r = .74$, $P < .001$), level of obstructive disease (forced expiratory volume in first second percent predicted, $r = .62$, $P < .001$), and dyspnea (Functional Status and Dyspnea Questionnaire, dyspnea over the past 30 days, $r = -.29$; $P < .05$) provide support for concurrent validity in people with chronic illnesses [44]. Successful use of wrist actigraphy to quantify physical activity has been reported in several recent studies involving people with cancer, including HCT patients [8,45-47].

The Godin leisure-time exercise questionnaire was used to assess self-reported physical activity in terms of usual leisure time exercise behaviors [42]. This brief, self-report, 4-item instrument assesses the frequency of periods of strenuous, moderate, and light activities greater than 15 minutes in duration during a typical 7-day period. The instrument was modified to include questions regarding average duration [48]. The instrument has established test-retest reliability [42]. Large correlations between the accelerometers and the Godin leisure-time exercise questionnaire provide support for convergent validity [49,50].

Fatigue

Fatigue was measured with the Chalder fatigue scale [51] and fatigue subscale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (described below) [52]. The Chalder fatigue scale is a multidimensional, self-report instrument that measures physical and mental fatigue using a 4-point Likert scale. Higher scores indicate greater fatigue. The 11-item instrument has excellent psychometric properties and has been successfully used in hospitalized and community-dwelling subjects, including those with hematological malignancies [53,54]. Normative mean scores for the overall fatigue score have been reported as 12.2
(SD = 4.0) in the general Norwegian population [55]. The fatigue subscale of the EORTC QLQ C-30 (3 items) measures physical fatigue using a 4-point Likert scale. The EORTC QLQ C-30 is described in detail below. The fatigue subscale has been used extensively in people with cancer and has established reliability and validity [56].

Muscle strength

Three tests of muscle mass and strength were performed: ultrasonic measurement of the cross-sectional area of the rectus femoris, hand grip strength, and arm curl test.

Rectus femoris cross-sectional area. The rectus femoris cross-sectional area was measured using the SonoSite M-Turbo ultrasound system (FUJIFILM SonoSite, Inc., Bothell, WA). To assess rectus femoris cross-sectional area, subjects were positioned using a standardized procedure (supine with arms resting comfortably at their sides, pillow behind head, head of bed elevated to 20°, and legs relaxed with knees extended) [57]. The distance between the anterior superior iliac spine and the upper pole of the patella was measured in centimeters. Using the superior iliac spine as the starting reference point, the skin was marked with a pen at 75% of this distance on the dominant leg [58]. This ink line served as a visual aid for the point of ultrasound measurement. Placing the transducer perpendicular to the skin along the longitudinal aspect of the thigh at the 75% mark, the rectus femoris was located. This location was chosen as the most proximal position on the thigh where the rectus femoris would be visualized in all subjects using the

linear transducer [59]. Subjects were asked to tense the muscle so that the rectus femoris was clearly identified and then relax the muscle completely. With the rectus femoris relaxed, 6 consecutive 2-dimensional images were taken. The cross-sectional area of the rectus femoris was obtained through manual tracing of the muscle borders using the SonoSite M-Turbo software.

As a proxy measure for muscle strength, ultrasound measurement of the rectus femoris has been significantly correlated with isometric maximum voluntary contraction in healthy subjects ($r = .80$, $P < .001$) and people with chronic obstructive pulmonary disease ($r = .78$, $p < .001$) [60]. Ultrasound measurement of the quadriceps has been used to successfully document significant declines in rectus femoris muscle mass after 1 week of leg immobilization in people with knee injuries ($P < .001$), followed by significant increases in muscle mass after rehabilitation ($P < .01$) [61]. Ultrasound measures are strongly correlated with the gold standard magnetic resonance imaging rectus femoris cross-sectional area (rho = .88) [62].

Hand grip strength. Hand grip strength was measured using a Jamar dynamometer (TEC, Clifton, NJ). Testing was performed with subjects sitting with the shoulder adducted and neutrally rotated. The elbow was flexed at 90° with the forearm in a neutral position and the wrist between 0° and 30° with 0° and 15° ulnar deviation, according to recommendations [63]. The results are reported as the mean of the 3 trials for the dominant hand [64]. Reported test-retest reliability coefficients for hand grip strength were .91 for men and .94 for women [65]. Hand grip strength was validated as an indicator of upper extremity strength by strong correlations between hand grip strength and forearm muscle area ($r = .73$), upper arm muscle area ($r = .71$), and total muscle mass ($r = .65$) [66-68].

Arm curl test. Upper body strength was measured with the 30-second arm curl test. Subjects were instructed to complete as many arm curls as possible in 30 seconds using the dominant arm. Men used an 8-pound weight and females used a 5-pound weight. The arm curl test has been used as part of the Senior Fitness Test [69,70]. The 30-second arm curl test has a moderately strong correlation with the chest press and is a valid surrogate for upper body strength in frail individuals [71].

Functional ability

Four objective functional ability tests were performed: timed stair climb, the timed up and go test, 15-foot walk time, and 30-second chair-stand test.

Timed stair climb. The timed stair climb was used as an indicator of lower body strength [72]. Subjects were timed with a digital stopwatch as they ascended a flight of 9 steps. Results are reported in seconds to reach the top of the flight of stairs. The timed stair climb has excellent test-retest reliability (r = .94) [73]. The results for timed stair climbs have been significantly correlated with isokinetic strength measurement of knee flexors and extensors [74].

Timed up and go test. The timed up and go test was used as a measure of basic functional mobility [75]. The timed assessment begins with individuals sitting down in a standard chair, rising, walking 8 feet, turning around and returning, then sitting down again. The test demonstrates strong reliability with intraclass correlations ranging from .93 in healthy adults [76] to .96 in community dwelling elders [77]. The test discriminates between those with worse home independence and increased risk for falls providing support for construct validity [77,78]. The test has been used successfully in people with cancer [79].

Fifteen-foot walk time. The 15-foot walk time test (4.57 meters) was used as an indicator of gait speed. Gait speed was determined by the number of seconds it took to walk 15 feet [80]. Subjects started in a standing position and were instructed to walk as quickly and safely as possible pass the 15-foot line, marked clearly with tape. Timing started when the foot first passed the start line and ended when both feet passed the 15-foot line. Subjects were told that they should only slow down after passing the line. Subjects were allowed to use assistive devices, such as canes. Four-meter gait speed has excellent reliability and validity in older adults [81] and those with chronic obstructive pulmonary disease [82]. The 4-meter gait speed is highly correlated with incremental shuttle walk and the 10-meter walk test, providing support for concurrent validity.

Thirty-second chair-stand test. The 30-second chair-stand test was conducted as an indicator of lower body strength. The 30-second chair-stand test involves recording the number of stands (sitting in a chair to standing erect) that a subject can complete in 30 seconds. Good stability and reliability have been reported in community-residing older adults, with test-retest correlations of .84 for men, .92 for women, and no significant changes in scores over a 2-day period [83]. The 30-second chair-stand test was validated as an indicator of lower body strength with moderate correlations between the chair-stand test and the 1-repetition maximum weight-adjusted leg-press performance ($r = .78$ men and .71 women). Chair-stand performance was able to discriminate between lower-active participants and higher-active participants ($P < .0001$), providing support for construct validity through contrasted groups. The 30-second chair-stand test is included in the Senior Fitness Test [69,70].

QOL

The EORTC QLQ C-30 was used to measure QOL [52]. The EORTC QLQ-C30 (version 3.0) is a 30-item tool consisting of (1) 5 functional scales (physical, role, emotional, cognitive, and social); (2) a global QOL/health status scale; (3) 3 multi-item symptom scales (fatigue, pain, and nausea and vomiting); and (4) a number of single-item questions (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial impact) [56]. Twenty-eight items use a 4-point Likert scale. The global QOL/health status scale employs a 7-point Likert scale, with 1 being very poor and 7 being excellent. Items on the multi-item subscales are averaged and then converted to a 0-to-100 scale. Higher scores on the 5 functional scales and the global QOL/health status scale represent higher levels of functioning. Higher scores on the symptom scales and the single-item questions indicate higher degrees of symptomatology. The EORTC QLQ-C30 is a well-established and psychometrically sound instrument used worldwide in clinical trials involving people with cancer [56]. High internal consistency has been reported for all of the multi-item subscales, including the global QOL subscale (range, .80 to .94) [52,84,85].

Data Collection Schedule and Procedures

Before hospitalization for HCT (baseline)

Wrist actigraphs were placed on the patient's nondominant hand to measure physical activity. The subjects were instructed to leave the device in place for the next 5 days. Subjects were instructed to carry on with normal activities, including bathing and showering, as the Actical is water-resistant. At the end of the 5-day period, subjects completed the 3 muscle strength tests, 4 functional ability tests, and the self-report questionnaires. The questionnaires were administered via interview. The muscle strength and functional ability tests took approximately 30 minutes to complete and the questionnaires took approximately 15 minutes.

After Intervention (during the seventh week after hospital discharge)

The procedures for data collection after intervention were the same as described for baseline.

Data Analysis

All data analyses were performed using SPSS (Version 22, IBM Corp., Chicago, IL). Descriptive statistics were calculated for all measures. Internal consistency estimates (Cronbach's alpha) were assessed for all multi-item Likert items (EORTC QLQ-C30). Split plot analysis of variance (2×2) was used to examine the effects of (1) group assignment (STEER compared to UC + AC with HE); (2) time (baseline [before HCT] and after intervention, during the seventh week after hospital discharge to coincide with completion of the intervention); and (3) the group × time interaction on physical activity, fatigue, muscle strength, functional ability and QOL. The expected data trends were as follows: (1) both groups (STEER and the UC + AC with HE) would be similar at baseline; (2) the 2 groups would be significantly different after intervention; (3) the STEER group would improve over time or remain stable; and, (4) the UC + AC with HE would decline over time or not change.

RESULTS

Demographic and Clinical Characteristics

Table 1 displays the demographic and clinical treatment information. The data presented represent the 67 study participants who were randomly assigned to a group, underwent HCT, and completed baseline and postintervention testing. Subjects ranged in age from 19 to 73 (mean, 53.3; SD, 12.2). The sample was racially diverse, composed of African Americans (n = 26, 39%); Caucasians (n = 30, 45%); and Latino, Hispanic, or Mexican American (n = 10; 15%). More males (n = 41; 61%) enrolled than females (n = 26; 39%). The majority were married (n = 30; 45%) and completed some college as their highest level of education (n = 27; 40%). Over 40% reported incomes less than $30,000 annually. All subjects received HCT for treatment of an underlying malignancy. Thirty-nine subjects (58%) received an autologous transplant

Table 1
Demographic and Clinical Characteristics (n = 67)

Characteristics	Value		
	STEER (n = 33)	UC + AC with HE (n = 34)	Total (n = 67)
Age, mean (SD)	51.9 (12.7)	54.6 (11.6)	53.3 (12.2)
Gender, N (%)			
Male	20 (61)	21 (62)	41 (61)
Female	13 (39)	13 (38)	26 (39)
Race, N (%)			
African American	14 (42)	12 (35)	26 (39)
White	14 (42)	16 (47)	30 (45)
Hispanic	4 (12)	6 (18)	10 (15)
Other	1 (3)	0	1 (1)
Marital status, N (%)			
Never married	6 (18)	10 (29)	16 (24)
Married	18 (55)	12 (35)	30 (45)
Divorced	6 (18)	6 (18)	12 (18)
Separated	2 (6)	3 (9)	5 (7)
Widowed	1 (3)	3 (9)	4 (6)
Education level, N (%)			
High school or less	11 (33)	11 (33)	22 (33)
Some college	15 (46)	12 (35)	27 (40)
Graduated from college	5 (15)	5 (14)	10 (15)
Graduate education after college	2 (6)	6 (18)	8 (12)
Annual family income, N (%)			
< $30,000	14 (42)	15 (45)	29 (43)
$31,000-$60,000	10 (30)	7 (21)	17 (25)
> $60,000	9 (27)	12 (35)	21 (31)
Diagnosis, N (%)			
Acute lymphoblastic leukemia	2 (6)	2 (6)	4 (6)
Acute myelogenous leukemia	7 (21)	7 (20)	14 (21)
Chronic lymphocytic leukemia	1 (3)	1 (3)	2 (4)
Chronic myelogenous leukemia	2 (6)	1 (3)	3 (4)
Hodgkin lymphoma	2 (6)	0	2 (3)
non-Hodgkin lymphoma	5 (15)	3 (9)	8 (12)
Multiple myeloma	12 (36)	16 (47)	28 (42)
Myelodysplastic syndrome	2 (6)	4 (12)	6 (8)
Donor type, N (%)			
Autologous	20 (61)	19 (56)	39 (58)
Sibling	4 (31)	6 (40)	10 (36)
Matched unrelated donor	8 (61)	8 (53)	16 (57)
Haplo-identical	1 (8)	1 (7)	2 (7)
Length of hospitalization (HCT to discharge, mean (SD)	16.7 (4.2)	18.1 (5.5)	17.4 (4.9)
No. (%) of subjects readmitted to hospital during post-hospital intervention phase	3 (9%)	8 (23%)	11 (16%)

(STEER group = 20; UC + AC with HE group = 19). Twenty-eight subjects received an allogeneic transplant (STEER group = 13; UC + AC with HE group = 15). There were no differences between groups on any of the demographic data or clinical characteristics. The means and standard deviations for physical activity, fatigue, muscle strength, and functional ability are presented in Table 2 and QOL variables in Table 3.

Compliance with STEER and UC + AC with HE

Subjects assigned to the STEER arm were asked to complete 18 moderate-intensity strength training sessions after hospitalization (approximately 1 supervised session per week depending on scheduled clinic visits and 2 unsupervised visits per week for 6 weeks for a total of 18 sessions). The mean compliance rate for exercise session completion was 83%. Seventy-two percent of subjects (n = 24) completed between 80% and 100% of sessions. Only 1 subject failed to complete any of the exercise sessions after hospital discharge. Three subjects completed between 40% and 59% of sessions and 5 completed between 60% and 79%. Subjects assigned to the UC + AC with HE were asked to complete 6 educational sessions (1 session per week for 6 weeks). The mean compliance rate for the health education sessions was 97%. Ninety-one percent (n = 31) completed all 6 educational sessions. One subjected completed 3 educational sessions, 1 completed 4, and 1 completed 5.

Physical Activity

Objectively measured physical activity

The main effects of group, F (1, 65) = 3.913, $P = .05$, and time, F (1, 65) = 12.210, $P = .001$, were significant. The STEER group was significantly more physically active than the UC + AC with HE group. Subjects in both groups experienced a significant reduction in physical activity baseline compared with after intervention. The STEER group experienced a 15% reduction in physical activity whereas the UC + AC with HE group experienced a 25% reduction, resulting in a 10% difference between the 2 groups. The group × time interaction was not significant, F (1, 65) = .295.

Self-reported physical activity

The main effects of group, F (1, 65) = .877; time, F (1, 65) = 1.151; and group × time, F (1, 65) = .502, were not significant.

Fatigue

Overall fatigue

The group × time interaction effect for overall fatigue was significant, F (1, 65) = 4.380, $P = .04$ (Figure 2). Tests of simple main effects revealed that the UC + AC with HE reported significantly increased overall fatigue from baseline to after intervention, t (33) = –2.174, $P = .04$, while the STEER group reported improvements in fatigue from baseline to after intervention, although this was not significant. The main effects of group, F (1, 65) = .005, and time, F (1, 65) = .355, were not significant.

Mental fatigue

Mental fatigue followed a similar pattern. The group × time interaction effect for mental fatigue was significant, F (1, 65) = 6.524, $P = .01$, (Figure 2). Tests of simple main effects revealed that the STEER group reported significant improvements in mental fatigue baseline to after intervention, t (32) = 2.131, $P = .04$, while the UC + AC with HE reported increased fatigue from baseline to after intervention although this was not significant. The main effects of group, F (1, 65) = .313; and time, F (1, 65) = .245, for mental fatigue were not significant.

Physical fatigue

The main effects of group, F (1, 65) = .049; time, F (1, 65) = 2.114; and, group × time interaction, F (1, 65) = 1.921, for physical fatigue were not significant.

Fatigue subscale of the EORTC QLQ C-30

The main effects of group, F (1, 65) = .003; time, F (1, 65) = 1.704; and group × time interaction, F (1, 65) = .174, for

Table 2
Means (SD) of Physical Activity, Fatigue, Muscle Strength, and Functional Ability; STEER (n = 33) compared to UC + AC with HE (n = 34)

Variable	Baseline Mean (SD)	Post Intervention Mean (SD)	Group Effect *P* Value	Time Effect *P* Value	Interaction Effect *P* Value
Physical activity					
Self-reported physical activity (Godin)			NS	NS	NS
STEER	18.8 (15.9)	28.2 (25.0)			
UC + AC with HE	27.6 (40.6)	29.5 (35.1)			
Physical activity (average physical activity count per minute)			.05	.001	NS
STEER	214 (131)	182 (113)			
UC + AC with HE	173 (97)	129 (83)			
Fatigue					
Overall fatigue (Chalder fatigue scale)			NS	NS	.04
STEER	16.9 (6.1)	16.3 (4.9)			
UC + AC with HE	15.8 (4.7)	17.6 (5.9)			
Physical fatigue (Chalder fatigue scale)			NS	NS	NS
STEER	11.7 (4.3)	11.7 (3.9)			
UC + AC with HE	10.9 (3.5)	12.1 (4.5)			
Mental fatigue (Chalder fatigue scale)			NS	NS	.013
STEER	5.2 (2.4)	4.5 (1.9)			
UC + AC with HE	4.9 (2.3)	5.4 (2.4)			
Fatigue (EORTC QLQ-C30)			NS	NS	NS
STEER	38.7 (28.9)	41.8 (24.9)			
UC + AC with HE	37.6 (25.2)	43.5 (26.9)			
Muscle strength					
Rectus femoris cross-sectional area, cm^2			NS	NS	NS
STEER	2.94 (1.17)	2.89 (1.13)			
UC + AC with HE	2.65 (1.15)	2.57 (1.13)			
Hand grip strength, kgs)			NS	< .001	NS
STEER	34.06 (10.74)	31.12 (10.26)			
UC + AC with HE	31.37 (10.58)	27.54 (11.07)			
Arm curl test (repetitions in 30 seconds)			.099	NS	.067
STEER	17.46 (6.05)	18.03 (6.01)			
UC + AC with HE	16.29 (4.67)	14.97 (5.45)			
Functional ability					
Timed stair climb, seconds			.074	.012	.029
STEER	5.54 (2.81)	5.72 (2.25)			
UC + AC with HE	5.56 (1.79)	8.11 (5.63)			
Timed up and go test, seconds			.05	NS	.05
STEER	7.31 (2.16)	7.18 (1.89)			
UC + AC with HE	7.86 (1.90)	10.11 (7.28)			
Fifteen-foot walk time, seconds			.038	.083	.083
STEER	3.28 (1.01)	3.27 (.86)			
UC + AC with HE	3.50 (.73)	4.10 (1.92)			
Thirty-second chair stand test, cycles in 30 seconds			NS	NS	NS
STEER	13.03 (4.97)	13.03 (5.58)			
UC + AC with HE	11.47 (6.37)	10.44 (6.73)			
Body weight, kilogram			NS	NS	NS
STEER	83.92 (22.73)	79.12 (22.70)			
UC + AC with HE	84.30 (24.54)	79.56 (24.09)			

NS indicates nonsignificant.

the fatigue subscale of the EORTC QLQ C-30 were not significant.

Muscle Strength

Rectus femoris cross-sectional area

The main effects of group, F (1, 65) = 1.213; time, F (1, 65) = 1.639; and group × time interaction, F (1, 65) = .124, for the rectus femoris cross-sectional area were not significant.

Hand grip strength

The main effect of time was significant, F (1, 65) = 33.556, $P < .001$. Both groups experienced reductions in hand grip strength from baseline to after intervention. The main effects of group, F (1, 65) = 1.528, and group × time interaction, F (1, 65) = .581, for hand grip strength were not significant.

Arm curls

The main effects of group, F (1, 65) = 2.801; time, F (1, 65) = .537; and group × time interaction, F (1, 65) = 3.464, $P = .067$, for arm curls were not significant. The group × time interaction effect approached significance, so tests of simple effects were performed. The STEER group was able to perform significantly more arm curls compared with the UC + AC with HE after intervention, t (65) = 3.05971, $P = .03$.

Functional Ability

Timed stair climb

The main effects of time, F (1, 65) = 6.643, $P = .01$, and group × time interaction, F (1, 65) = 5.014, $P = .03$, for the timed stair climb were significant (Figure 3). Test of simple main effects revealed that the UC + AC with HE group's timed stair climb was significantly slower from baseline to after intervention, t (33) = –2.644, $P = .01$, while the STEER group's time remained stable. Although there was no significant difference between groups at baseline, the STEER group was able to climb the stairs significantly faster after the intervention, t (44) = 2.293, $P = .03$. The group effect was not significant, F (1, 65) = 3.308.

Table 3
Means (SD) of QOL (EORTC QLQ C-30)

QOL Variable	Baseline	After Intervention
Global QOL/health status		
STEER	62.1 (22.7)	64.4 (18.2)
UC + AC with HE	61.5 (21.0)	62.5 (24.9)
Functional subscales		
Physical		
STEER	78.6 (26.2)	79.4 (18.9)
UC + AC with HE	79.2 (18.1)	74.9 (20.2)
Emotional		
STEER	71.7 (25.3)	79.3 (23.9)
UC + AC with HE	74.0 (21.2)	74.0 (25.4)
Role		
STEER	70.2 (32.2)	74.7 (28.3)
UC + AC with HE	65.7 (31.2)	74.5 (32.4)
Cognitive		
STEER	83.3 (21.7)	86.9 (17.6)
UC + AC with HE	84.3 (17.9)	78.9 (22.1)
Social		
STEER	67.7 (33.1)	72.2 (31.1)
UC + AC with HE	74.5 (26.7)	70.1 (31.7)
Symptoms subscales		
Pain		
STEER	26.8 (27.9)	25.3 (31.8)
UC + AC with HE	33.8 (30.3)	34.8 (33.7)
Nausea/vomiting		
STEER	8.1 (22.1)	17.7 (29.7)
UC + AC with HE	10.3 (18.4)	10.3 (19.3)
Single items		
Appetite loss		
STEER	20.2 (31.1)	22.2 (33.0)
UC + AC with HE	20.6 (26.0)	28.4 (35.9)
Constipation		
STEER	11.1 (27.2)	8.1 (22.1)
UC + AC with HE	8.8 (17.0)	9.8 (19.3
Dyspnea		
STEER	23.2 (35.8)	20.2 (28.8)
UC + AC with HE	18.6 (24.9)	21.6 (25.8)
Diarrhea		
STEER	14.1 (28.9)	10.1 (17.6)
UC + AC with HE	11.8 (25.8)	11.8 (27.1)
Financial impact		
STEER	39.4 (32.8)	28.3 (36.4)
UC + AC with HE	33.3 (41.0)	29.4 (36.5)
Sleep disturbances		
STEER	32.3 (36.8)	37.4 (38.9)
UC + AC with HE	43.1 (35.3)	39.2 (37.1)

Data presented are mean (SD).

Timed up and go

The main effects of group, F (1, 65) = 4.885, $P = .03$, and group × time interaction, F (1, 65) = 3.940, $P = .05$, for the timed and up were significant (Figure 3). Test of simple main effects revealed that the UC + AC with HE group was slower from baseline to after intervention (approached significance), t (33) = –1.921, $P = .06$, while the STEER group's time remained stable. After the intervention, the STEER group was able to complete the timed up and go test faster than the UC + AC with HE, t (46) = 2.274, $P = .03$. There was no significant difference between groups at baseline. The time effect was not significant, F (1, 65) = 3.133.

Fifteen-foot walk time

The main effect of group, F (1, 65) = 4.481, $P = .04$, was significant. The STEER group completed the 15-foot walk time faster. The main effects of time, F (1, 65) = 3.095, and group × time interaction, F (1, 65) = 3.108, were not significant. The time and group × time interaction effects approached significance ($P = .08$). As a result, test of simple effects were conducted. The UC + AC with HE group's walk time was slower, approaching significance, from baseline to after intervention, t (33) = –1.921, $P = .06$. There was no significant difference in walk time for the STEER group baseline to after intervention. At baseline, no significant differences between groups were detected. After the intervention, the STEER group was significantly faster than the UC + AC with HE, t (46) = 2.274, $P = .02$.

Thirty-second sit to stand

The main effects of group, F (1, 65) = 2.337; time, F (1, 65) = .946; and group × time interaction, F (1, 65) = .946, for the 30-second sit to stand were not significant.

QOL

Means and standard deviations for the global QOL subscale, 5 functional subscales, 3 symptom subscales, or single items are displayed in Table 3. None of these resulted in significant group, time, or group × time interaction effects.

DISCUSSION

Intensive cancer treatment followed by HCT is potentially curative but associated with substantial short- and long-term adverse effects. Effective pragmatic interventions during the early recovery period are urgently needed to alleviate

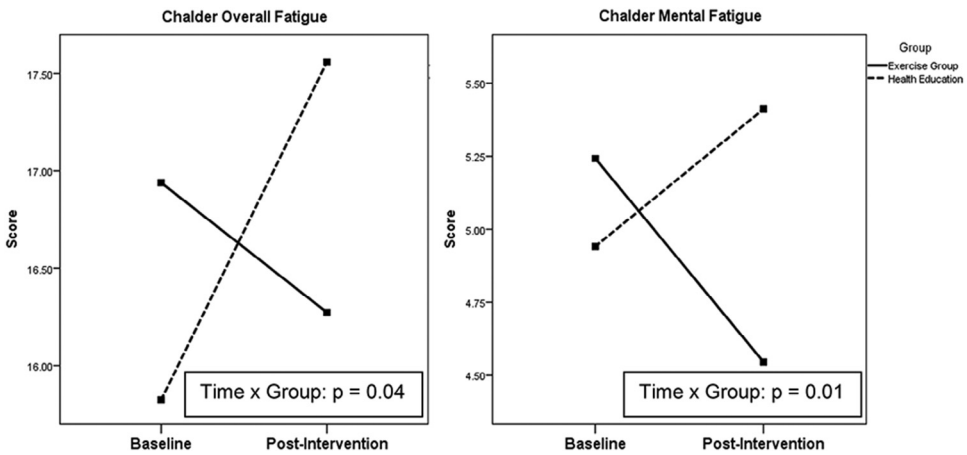

Figure 2. Fatigue.

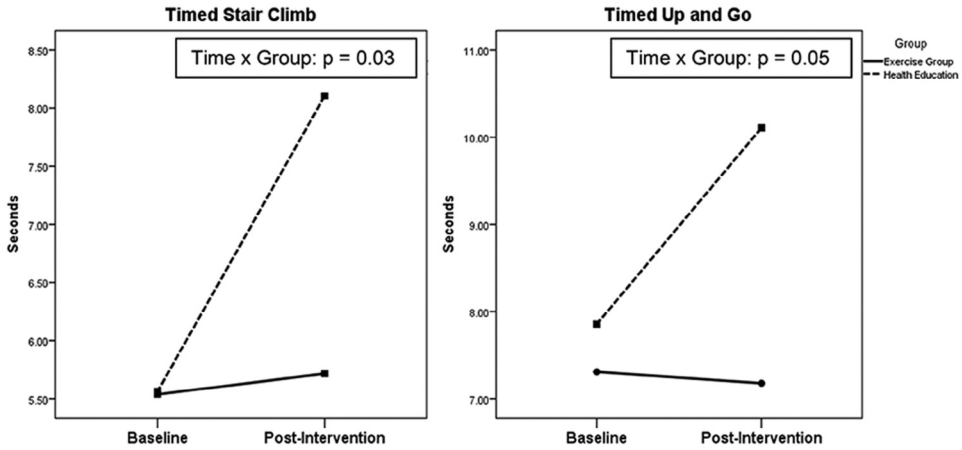

Figure 3. Functional ability.

symptoms, promote functional independence, and improve QOL. The findings from this single-blind RCT demonstrate the beneficial effects of a strength training program after HCT on physical activity, fatigue, muscle strength, and functional ability compared with UC + AC with HE. Importantly, these positive effects were demonstrated while controlling for the time, attention, and interpersonal communication received by the STEER group through the use of an appropriate control group. The findings provide support for our model that maintaining muscle mass through strength training effectively reduces fatigue and maintains and/or improves muscle strength and functional ability after intensive cancer treatment and HCT. Although the exact recovery patterns between groups and over time varied, the STEER group either maintained or improved their health status from baseline to after intervention whereas the US + AC with HE group generally declined over time.

This study, focused solely on strength training during the acute recovery period, contributes to a growing body of exercise research after HCT and addresses a known gap in the literature. To demonstrate the effectiveness of strength training, we hypothesized that significant group × time interactions would be found. As expected, strength training preferentially improved fatigue and functional ability (timed stair climb and timed up and go) as demonstrated by the significant interactions effects with trends toward improving muscle strength (arm curls). This provides evidence that a 6-week moderate-intensity strength training program may be a viable option for enhancing early recovery after HCT. The findings are novel as only 1 RCT, besides our pilot work, tested single-modality strength training [28]. The Cunningham study did not assess fatigue or functional ability and the exercise intervention focused on inpatient strength training (up to day 35 after transplantation).

We expected to find significant interaction effects for physical activity, muscle strength (cross-sectional area of the rectus femoris and hand grip) and QOL. We found the following: (1) group and time effects for physical activity, (2) time effects for hand grip strength, and (3) no effects for QOL or changes in muscle mass as measured by the rectus femoris cross-sectional area. As expected, the STEER group was more physically active as demonstrated by the group effect and only experienced a 15% decline in physical activity after intervention compared with a 25% drop in the control group. A significant interaction effect, however, was not found. There are several potential reasons for this. First, our strength training intervention may not have been strong enough to produce a significant interaction effect. Second, objective physical activity may not be captured adequately by wearing devices on the wrist. Third, the control group may have consciously attempted to increase physical activity levels in the post-transplantation period as evidenced by their reports of leisure-time physical activity. The control group reported more leisure-time physical activity at baseline and after intervention compared with the strength training group. The results from the objective physical activity assessments, however, indicate that the strength training group was more physically active. The reasons for the discrepancy between objectively measured and self-reported physical activity is not clear but requires further investigation. Importantly, subjects assigned to the control group were not told that they could not exercise as this would have been unethical. Finally, the intervention may have no effect on physical activity as the main effect of strength training is to build and/or maintain muscle strength.

The results for increasing physical activity through exercise in the HCT literature are mixed. Consistent with our findings, Knoll et al. reported that a 12-week outpatient exercise program, incorporating aerobic and strength exercises, compared with usual care did not result in a group × time interaction effect for self-reported physical activity [21]. Conversely, Jacobsen et al. conducted a large (n = 711) 4-arm study comparing a self-directed exercise program with a self-administered stress management program, a self-directed exercise program plus self-administered stress management, and usual care [86]. The exercise intervention was self-directed after a brief 20-minute introduction to the program. Those assigned to the exercise group increased their physical activity (as measured by the leisure score of the Godin leisure-time exercise questionnaire) 6 months after the intervention but not at day 30, 60, or 100. The reason for the delayed response is not clear. Although it seems logical that exercise would lead to increased physical activity, the mixed results suggest that further research is needed. In addition, it would be prudent to collect self-reported as well as objectively measured physical activity given the discrepancies between the 2 in our study.

HCT recipients represent an understudied group even though they may be one of the neediest, in terms of physical deconditioning after cancer treatment. Two meta-analysis

evaluating exercise after HCT identified positive effects across a range of potential outcomes, such as fatigue, muscle strength, and QOL [18,19]. These analyses, however, only included 8 [18] and 11 [19] RCTs, demonstrating the continued need for investigation. Furthermore, small sample sizes, heterogeneity of exercise interventions, timing differences related to exercise initiation, among other factors, make it very difficult to effectively combine results across studies; and, ultimately identify the pillars of an ideal exercise program after HCT. An exercise program for people in the acute recovery phase may need to be vastly different than that developed for long-term survivors.

The importance of developing effective and pragmatic exercise interventions after HCT cannot be overstated to increase the likelihood of translation into clinical practice, if successful. Our STEER intervention is innovative as it was tested in a challenging group of patients during a period of complex and frequently changing health care needs and because it integrated seamlessly into existing clinical practice settings, which is unique and patient centered. Implementing an exercise program into any clinical practice is challenging and is even more so in this population. STEER was designed to maximize benefits and minimize burdens in research subjects by taking advantage of common clinical situations after HCT, such as frequent clinic visits during the first 6 weeks after hospital discharge and downtime in the clinic when waiting to see health care providers. Using the downtime in clinic to exercise after hospitalization is an efficient use of the subject's time that does not extend clinic visits and may increase patient satisfaction although we did not measure this. Elastic resistance bands were used instead of free weights as they are very portable and unlikely to cause harm if dropped. Self-efficacy to exercise was promoted by providing instruction and simulating the exercises without bands during hospitalization. This also helped build rapport with subjects before beginning the moderate-intensity strength training. The compliance with the moderate-intensity program conducted after hospital discharge was high (83%), demonstrating acceptability of the intervention and effective tailoring to the subject's capabilities. In this study, our goal was to a balance between intensity of the intervention, making it strong enough to exert an effect on important variables, such as fatigue and functional ability, yet simple enough for eventual scalability.

This study findings provides direction for multiple avenues of scholarship. Continuing this line of inquiry, further research is needed, such as testing STEER in larger samples, across multiple sites and monitoring subjects over longer periods of time to determine sustainability of effects. Our study only followed subjects to the end of the 6-week intervention; this is a limitation of our study. In our next study, we plan to implement the intervention over 12 weeks and follow subjects for 6 months to determine the longer-term effects and sustainability of the strength training intervention. The use of different comparison groups may also influence study findings. In this study, we stringently controlled for the time, attention, and interpersonal communication received by the STEER group. Our control arm contained a potentially active ingredient, standardized health education, and this may have confounded our ability to find QOL effects. Compliance in the control arm was very high for the 6 educational sessions (over 97%), demonstrating acceptability. To promote high subject retention in the control group, as was the case in our study, it may be important that HCT subjects assigned to the control arm receive an intervention perceived to be valuable to their health, but this may come at the expense of finding significant results for important variables.

CONCLUSION

A moderate-intensity 6-week strength training intervention enhances early recovery after HCT; reducing fatigue while maintaining and/or improving muscle strength and function ability. The recovery patterns for the strength training and UC + AC with HE groups varied. The strength training group generally improved or stayed the same over time while the UC + AC with HE group generally declined. Significant differences between the groups were found after intervention. The strength training intervention, specifically designed to maximize benefits to subjects while minimizing burdens, was integrated seamlessly into existing clinical practice settings. A balanced approach to developing exercise interventions is needed for HCT recipients; making it strong enough to effect outcomes, simple enough to minimize subject burdens, and relatively straightforward and uncomplicated to facilitate translation into clinical practice.

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